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Dynamic modelling and simulation of reactive transport phenomena in an amperometric blood glucose biosensor

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Abstract

The treatment of diabetes as well as several other diseases which affect millions of patients worldwide strongly depend on deploying affordable technologies for frequent and accurate monitoring of blood glucose concentrations. Both theoretical and experimental investigations of novel blood glucose biosensor concepts pave the way for fast efficiency analysis of candidate biosensor designs. Recent studies have addressed the operation of amperometric biosensors, within which a combination of an enzymatic reaction and an enzyme deposited on an electrode allows for conclusive blood glucose detection. This paper models a single droplet on blood on an amperometric glucose biosensor to investigate the sensitivity of sensor performance to varying transport phenomena parameter values. The work presents a comprehensive sensitivity analysis, based on a new two-dimensional spatiotemporal model (constructed in MATLAB) which studies the combined reactive transport phenomena within a blood droplet deposited on an enzyme-coated surface. The sensitivity analysis explores the variation of electrode response (current density) and concentration profiles throughout the droplet and the enzyme layer subject to varying initial conditions and component diffusivities. Results clearly indicate a strong dependence of output profiles on the said sensitivity parameters: ensuring high current density (especially for small droplet volumes) is a prerequisite for developing reliable glucose biosensors of high accuracy and precision.

Keywords: Modelling; simulation; diabetes; glucose; biosensors; reaction-diffusion.

1. Introduction

Approximately 5% of the UK population have some form of diabetes: many patients require home glucose biosensors (Peng et al., 2016). Diabetes treatment is dependent upon the availability of reliable and affordable technologies to monitor blood glucose levels. The development of low-cost but high-fidelity biosensors for blood monitoring is pivotal, especially for underprivileged communities and countries with growing populations but modest healthcare expenditure. Both theoretical and experimental investigations of novel blood glucose biosensor concepts are essential, particularly because the latter is essential to determine prior to industrial-scale production ventures (Cambiaso et al., 1996). Recent studies consider amperometric biosensors, in which an enzymatic reaction on an enzyme-coated electrode allows the measurement of blood glucose concentrations (Baronas and Kulys, 2008). Modelling and simulation allows the effects of many parameters to be studied with relative ease and speed compared to experimental methods. This paper models a single droplet of blood on an enzyme coated electrode, modelling a glucose biosensor. Sensitivity analyses of blood glucose concentration variation for different transport properties allows insight into essential design considerations for the development of high-fidelity glucose biosensors.

2. Sensor Model

The blood droplet contacts an enzyme coated electrode. It is assumed that blood droplet geometry remains fixed. The 2D model domain is split into two subdomains: the droplet and the enzyme, which are created in MATLAB using finite difference analysis.

2.1 System Geometry

The system is modelled as a half ellipse (the blood droplet) on a rectangle (the enzyme coating). Dimensions of the droplet and enzyme considered are shown in Fig. 1.

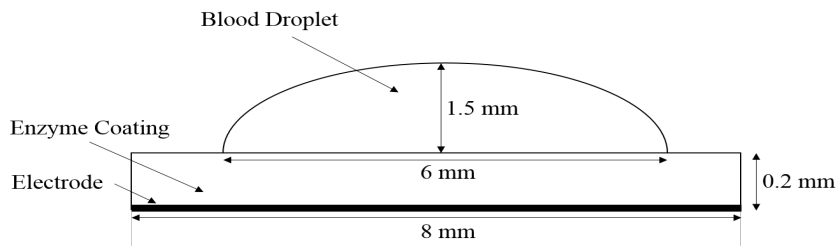
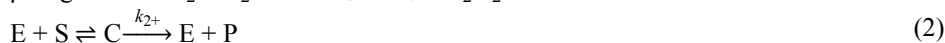
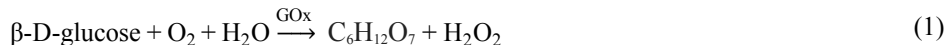


Figure 1: Geometry of a blood droplet on the enzyme-coated electrode of a glucose biosensor.

2.2 Enzymatic Reaction

The enzyme (Glucose Oxidase, GOx) is immobilised in the coating and catalyses the reaction of glucose to gluconic acid ($C_6H_{12}O_7$) and hydrogen peroxide (H_2O_2).



where E is the enzyme, C is the substrate-enzyme complex, S is the substrate (glucose) and P is product. Rate constants of the forward and backward reactions (Eq. 2) are k_{1+} and k_{2+} , respectively. Current is produced by the oxidation of H_2O_2 (Eq. 3).



2.3 Transport Phenomena: Partial Differential Equations (PDEs)

Reactant and product diffusion occurs in the blood droplet; chemical reaction only occurs at the enzyme layer. Mass transfer is modelled via Fick's second law of diffusion

$$\frac{\partial C_S}{\partial t} = D_{S,1} \nabla^2 C_S \quad (4)$$

$$\frac{\partial C_P}{\partial t} = D_{P,1} \nabla^2 C_P \quad (5)$$

where $D_{S,1}$ and $D_{P,1}$ are the diffusivities of S and P in the droplet, respectively, and C_S and C_P are the concentrations of S and P in the droplet respectively. Reaction occurs in the immobilized enzyme layer; concentrations obey the reaction-diffusion PDEs (eqs. 6-7).

$$\frac{\partial C_S}{\partial t} = D_{S,2} (\nabla^2 C_S) - \frac{V_{\max} C_S}{K_M + C_S} \quad (6)$$

$$\frac{\partial C_P}{\partial t} = D_{P,2} (\nabla^2 C_P) + \frac{V_{\max} C_S}{K_M + C_S} \quad (7)$$

where V_{\max} is the maximum enzymatic rate ($= k_{2+} C_S$), K_M is the Michaelis-Menten constant, $D_{S,2}$ and $D_{P,2}$ are the diffusivities of S and P in the enzyme, respectively.

2.4 Dimensionless model

We introduce the dimensionless parameters X , Y , T , \bar{S} and \bar{P} as the dimensionless 2D spatial coordinates (x and y), time coordinate (t), C_S and C_P , respectively. Dimensionless parameters are calculated as the ratio of the dimensional coordinate to a characteristic value. The reaction-diffusion PDE for glucose become dimensionless when substituted (eqs. 8-9). $L^* = 1$ mm, $T^* = 10$ s and $U^* = 4$ mmol L⁻¹ are the characteristic values for spatial coordinates, the time coordinate and concentrations, respectively.

$$\frac{\partial \bar{S}}{\partial T} = \frac{D_s}{L^{*2}} (\nabla^2 \bar{S}) - \frac{V_{\max} \bar{S}}{K_M + S^* \bar{S}} \quad (8)$$

$$\frac{\partial \bar{P}}{\partial T} = \frac{D_s}{L^{*2}} (\nabla^2 \bar{P}) + \frac{V_{\max} \bar{S}}{K_M + S^* \bar{S}} \quad (9)$$

2.5 Boundary Conditions

No flux conditions exist on the curved surface of the droplet, i.e. $\nabla \bar{S} = 0$, $\nabla \bar{P} = 0$. On the electrode, it is assumed that P is readily consumed (i.e. $\bar{P} = 0$) and there is a no flux condition for S. On the edges of the electrode, we assume $\bar{S} = 0$, $\bar{P} = 0$. Furthermore, we assume no flux conditions in the area of enzyme which is not contacting the droplet.

Table 1: Base-case kinetic and transport parameters and initial conditions for the model.

Parameter	Units	Value
k_{+1}	m ³ mol ⁻¹ s ⁻¹	1.20·10 ⁻²
k_{-1}	s ⁻¹	0.68·10 ⁻³
k_2	s ⁻¹	5.00·10 ⁻²
k_M	mol m ⁻³	4.22
E_0	mol m ⁻³	1.25·10 ⁻¹
V_{\max}	mol m ⁻³ s ⁻¹	6.30·10 ⁻³
$D_{S,\text{droplet}}$	m ² s ⁻¹	6.00·10 ⁻¹⁰
$D_{S,\text{enzyme}}$	m ² s ⁻¹	3.00·10 ⁻¹⁰
$D_{P,\text{droplet}}$	m ² s ⁻¹	6.00·10 ⁻¹⁰
$D_{P,\text{enzyme}}$	m ² s ⁻¹	3.00·10 ⁻¹⁰
C_{S0}	mmol L ⁻¹	4.00

3. Results and Discussion

Reaction kinetic and transport phenomena parameters and initial conditions (including the initial enzyme concentration, E_0) used as a base case in the model are shown in Table 1. The choice of initial glucose (substrate) concentration, C_S , is based on the minimum fasting blood glucose concentration for a healthy individual (Sarwar et al., 2010). Sensitivity analyses investigate the effect of varying reactant and product diffusivities in the droplet and enzyme layer and initial blood glucose concentration on the glucose biosensor electrode current density, as well as output reactant and product concentration profiles. Other parameters are kept constant for all sensitivity analyses.

Fig. 2 shows sensitivity analyses for the transient current density of the biosensor electrode. At low substrate diffusivities in the droplet ($D_{S,\text{droplet}}$), longer timescales are required for substrate to reach the enzyme layer and produce current (Eq. 3); consequently, a plateau in current density is gradually attained. For high $D_{S,\text{droplet}}$, substrate reaches the enzyme layer faster than it is reacted, leading to an initial peak in

current density followed by a gradual decrease. For low substrate diffusivities in the enzyme layer ($D_{S,\text{enzyme}}$), lesser enzyme layer surface areas are available for substrate reaction, and hence current density peaks are observed followed by gradual decline. As $D_{S,\text{enzyme}}$ increases, a greater surface area is available for reaction, and thus plateaus are gradually attained. As product diffusivities in the droplet ($D_{P,\text{droplet}}$) increase, less product produced in the enzyme layer occupies enzyme surface area for reaction, hence induced current densities increase. When product diffusivity in the enzyme layer ($D_{P,\text{enzyme}}$) is lower, less area is available for reaction, due to the lower propensity for product transport from enzyme, and longer times are required for maximum currents.

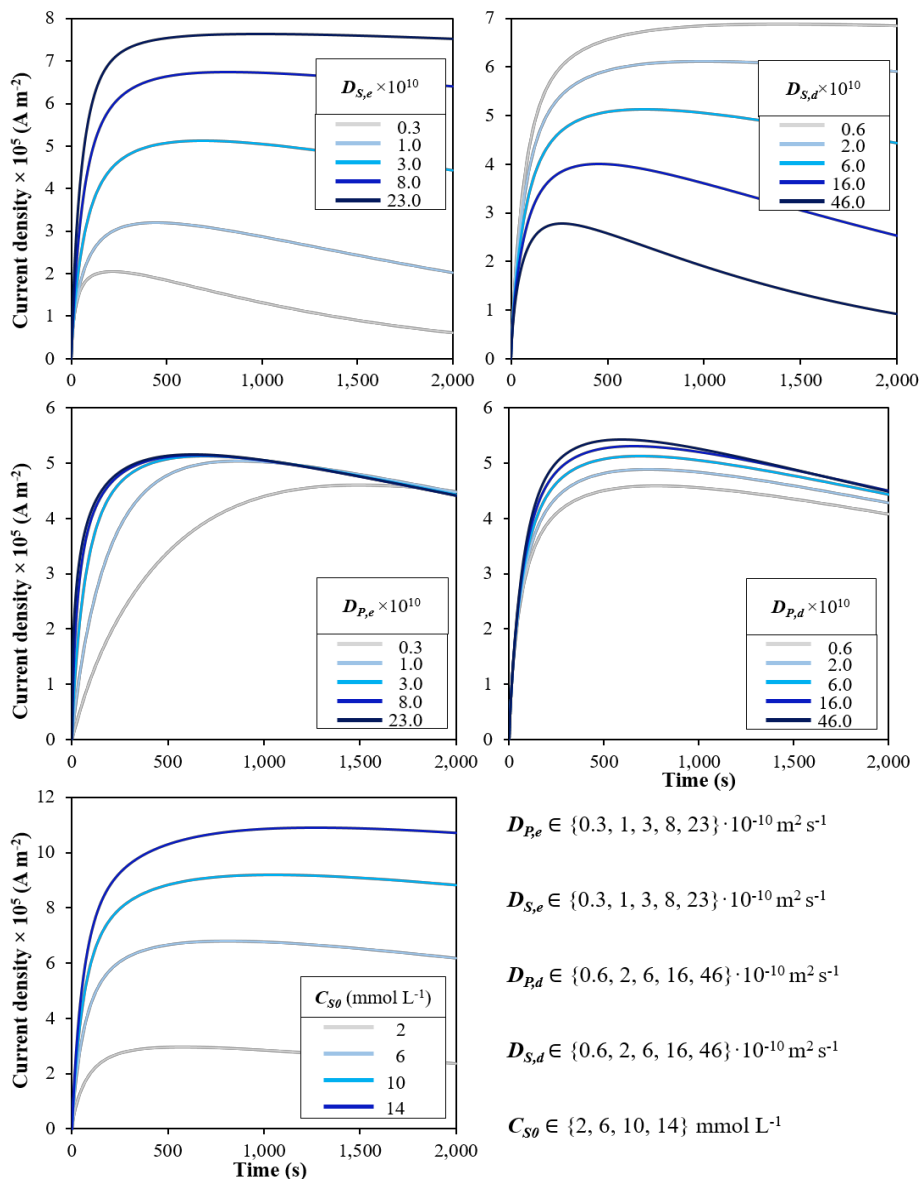


Figure 2: Effect of model parameters on transient biosensor electrode current densities.

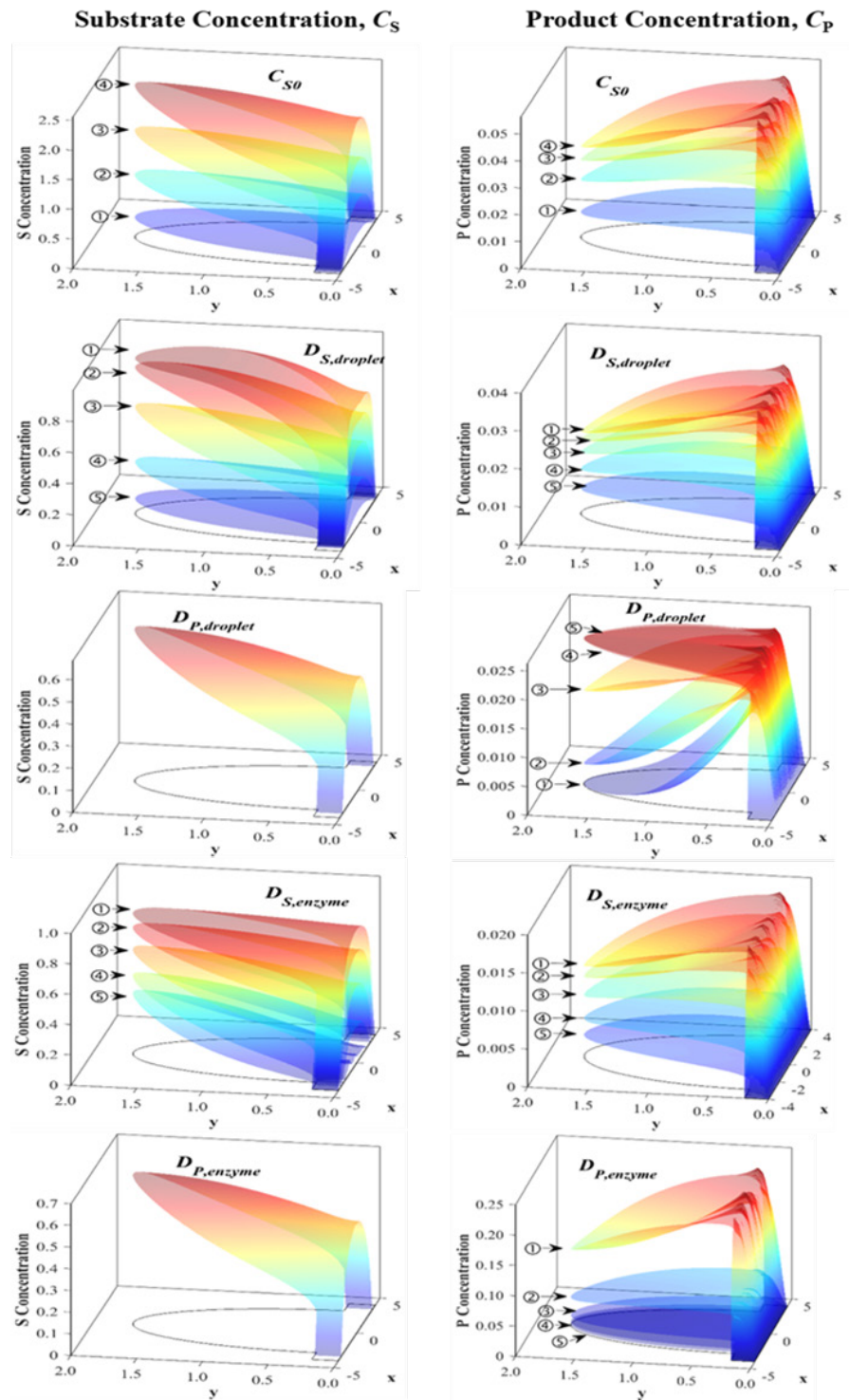


Figure 3: Sensitivity of output concentration profiles vs. model parameters (Table 2).

Table 2: Parameter variation for the model-based sensitivity analysis shown in Fig. 3.

Fig. 3 notation	C_{S0} (mmol L ⁻¹)	$D_{\text{enzyme}} \cdot 10^{10}$ (m ² s ⁻¹)	$D_{\text{droplet}} \cdot 10^{10}$ (m ² s ⁻¹)
①	2.0	0.3	0.6
②	6.0	1.0	2.0
③	10.0	3.0	6.0
④	14.0	8.0	16.0
⑤	—	23.0	46.0

Transient current densities illustrated in Fig. 3 clearly increase with initial blood glucose concentrations; greater initial substrate (glucose) concentrations incur greater amounts of H₂O₂, which thus induces greater current (eqs. 1-3). Current densities plateau beyond 500 s for all initial concentrations considered. Biosensor performance is strongly dependent on patient-to-patient physiological variability, as well as on the temperature dependence and sensitivity of hence varying enzymatic reaction kinetic parameters.

Fig. 3 shows the variation of substrate and product concentration profiles in the droplet with varying transport properties; parameter values associated with individual analyses are provided in Table 2. Increasing initial blood glucose concentrations lead to higher concentration profiles throughout the droplet. As substrate diffusivity in the droplet ($D_{S,\text{droplet}}$) increases, concentrations decrease throughout the droplet; expectedly, product concentrations decrease with increasing distance (y) from the enzyme layer. Increasing product diffusivity in the droplet ($D_{P,\text{droplet}}$) significantly affects profiles due to the effect of product diffusion on enzyme layer surface availability discussed previously. Increasing substrate diffusivities in the enzyme layer ($D_{S,\text{enzyme}}$) result in decreasing concentrations in the analysed blood droplet. Increasing product diffusivities in the enzyme layer ($D_{P,\text{enzyme}}$) incur rapidly decreasing product concentrations in the droplet due to the preferential diffusion of product in the enzyme layer to the blood droplet.

4. Conclusion

Numerical modelling of a blood droplet on a glucose biosensor with parametric sensitivity analysis has been conducted to investigate the sensitivity of glucose biosensor performance to essential operating parameters. Transient electrode responses (current densities) vary significantly with initial blood glucose concentration. Sensitivity analyses show larger electrode responses are gained for higher enzyme layer diffusivities. This work illustrates the importance of ensuring high current densities for effective biosensor performance and the potential for tuning enzyme layer properties for the design of high-fidelity glucose biosensors for their application in modern medicine.

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